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Original article

Synthesis and antitumor activity of novel dithiocarbamate substituted chromones

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ABSTRACT

A series of chromone derivatives bearing diverse dithiocarbamate moieties were designed and synthesized *via* a three-component reaction protocol. Their *in vitro* antitumor activities were evaluated by MTT method against HCCLM-7, Hela, MDA-MB-435S, SW-480, Hep-2 and MCF-7. Two compounds (3-chloro-4-oxo-4*H*-chromen-2-yl)methyl piperidine-1-carbodithioate (**Iq**) and (6-chloro-4-oxo-4*H*-chromen-3-yl)methyl piperidine-1-carbodithioate (**II**u), were identified as the most promising candidate due to their high potency and broad-spectrum. Further flow-activated cell sorting analysis revealed that compounds **Iq** and **II**u arrest the cell cycle of SW-480 and MDA-MB-435s both in G_2/M phase with dose-dependent effect and might display apoptosis-inducing effect on these tumor cell lines.

1. Introduction

As one of the most representative families of plant secondary metabolites, flavonoids have been found to be associated with a remarkable spectrum of biological activities [1–3]. In last decades, medicinal chemists have paid great attentions on the isolation, screening and structural modifications of new flavonoids. Most interestingly, it has been found recently that some flavonoids displayed anticancer activity with novel mechanisms, such as carcinogen inactivation, antiproliferation, cell cycle arrest, induction of apoptosis and differentiation, inhibition of angiogenesis, antioxidation and reversal of multidrug resistance [4]. To date, some flavonoids with novel action mechanism have entered clinical trials. For example, as shown in Fig. 1, flavopiridol was identified as the first cyclin-dependent kinase inhibitor and entered Phase II clinical trials [5].

Dithiocarbamate (DTC) derivatives are well known as organic intermediates, rubber additive, additive of polluted water, vulcanizing agents and fungicides [6]. As shown in Fig. 1, for example, DSF, an irreversible inhibitor of aldehyde dehydrogenase, is one of the two drugs approved by FDA for treatment of alcoholism [7]. Clinical trials have shown the efficacy of DSF without toxicity. In clinical trials DDTC was used in patients with HIV-1 infection and found to delay progression to AIDS. PDTC is a stable pyrrolidine derivative of dithiocarbamates and an antioxidant. Previous studies have shown that PDTC strongly inhibits replication of human rhinoviruses and coxsackievirus myocarditis. PDTC also showed inhibitory ability against murine colon adenocarcinoma bearing mice through the inhibition of nuclear factor κB in the tumor tissue [6,7]. Recently, Dou et al. reported that the DSF–Cu complex showed inhibition of proteasome activity and induction of apoptotic cell death [7].

Based on the above considerations, we proposed that chromones bearing DTC moiety should display some interesting anticancer activity. Therefore, we designed compounds **I**, **II**, **III** and **IV** as shown in Fig. 2 with the aim to discover lead structure with anticancer activity. Herein, we described the detailed synthetic route, screening results and structure–activity relationships of these designed compounds. Fortunately, two compounds with promising broad-spectrum anticancer activity were identified.

2. Results and discussion

2.1. Chemistry

The synthetic route for compound **I** is outlined in Scheme 1. According to the reported procedures [8,9], 2-methyl chromone **1** underwent bromination reaction with NBS to give the desired 2-bromomethyl chromone **2** in yields of 70–82%. Then, at the presence of potassium phosphate as base [10], a subsequent three-component reaction of the corresponding amine, carbon disulfide and the intermediate **2** produced compound **I** in good yields

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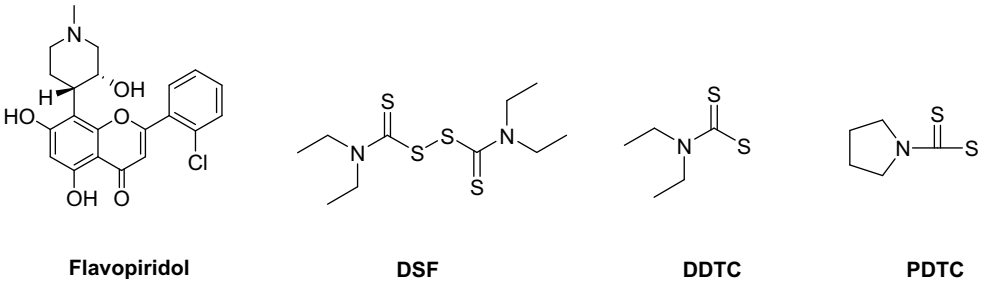

Fig. 1. Structures of flavopiridol and some representative dithiocarbamates.

(72–87%). As shown in Schemes 2 and 3, compounds **II** and **III** could be easily prepared by the similar three-component reaction using 3-cholоromethyl chromone **3** and 3-bromochromone **4** as substrate, respectively [11,12]. It should be noted that sodium methoxide rather than potassium phosphate was used as base for the three-component reaction of 3-bromochromone **4**. Scheme 4 showed the synthetic route of compound **IV**. The bromination of the starting material **5** with NBS afforded 6-bromomethyl chromone **6** smoothly in a yield of 80% [9]. Then, three-component reaction of the corresponding amine, carbon disulfide and intermediate **6** produced the desired compound **IV** in good yields (82–88%) when potassium phosphate was used as base.

The structures of all the target compounds were characterized by elemental analyses, ^{1}H NMR and EI-MS spectrum. In addition, the crystal structures of **I**c, **II**s and **III**b were determined by X-ray diffraction analyses [13]. As shown in Fig. 3, it can be found that the special tropism of DTC side chain shows big difference. The dihedral angles between the pyrone ring and DTC plane are 75.05° (**I**c), 36.61° (**II**s) and 78.67° (**III**b), respectively. The distance between the centroids of pyrone ring and DTC unit are 4.46 Å (**I**c), 4.65 Å (**II**s) and 3.91 Å (**III**b), respectively.

2.2. Pharmacology

The *in vitro* antiproliferative activities of the synthesized compounds **I**, **II**, **III**, and **IV** against six cancer cell lines, including HCCLM-7 (hepatoma carcinoma cell), Hela (cervical carcinoma cell), MDA-MB-435S (mammary adenocarcinoma cell), SW-480 (colon carcinoma cell), Hep-2 (laryngocarcinoma cell) and MCF-7 (mammary adenocarcinoma cell), were assayed by MTT method [14] and the results expressed as IC_{50} were summarized in Table 1.

As shown in Table 1, the substituent on benzene ring of compound **I** displayed remarkable effect on the antitumor activity. For the derivatives bearing the same DTC moiety, introduction of methoxyl group onto the position-7 always improved significantly the antitumor activity, such as compounds **I**a and **I**f, **I**c and **I**g, **I**d and **I**h. However, introduction of Cl atom onto the position-7 did not improve the activity. However, most interestingly, some compounds bearing a chlorine atom at 3-position were found to display good antitumor activities with broad-spectrum. For example, the IC_{50} values of compound **I**p range from 0.6 μM against Hep-2 to 2.3 μM against MCF-7. The IC_{50} values of compound **I**q are 0.77 μM, 0.69 μM, 0.94 μM and 1.0 μM against MDA-MB-435s, SW-480, Hep-2 and MCF-7, respectively.

In most cases, compound **II** except for **II**h and **II**i displayed higher antitumor activity than the corresponding compounds **I**. For example, compound **II**a and **I**a (R = H, D = D_2), **II**b and **I**b (R = H, D = D_3), **II**c and **I**c (R = H, D = D_4), **II**d and **I**d (R = H, D = D_5), **II**j and **I**f (R = 7-OMe, D = D_2), **II**l and **I**g (R = 7-OMe, D = D_4), **II**m and **I**h (R = 7-OMe, D = D_5), **II**t and **I**k (R = 7-OMe, D = D_3), **II**u and **I**l (R = 7-OMe, D = D_4), **II**v and **I**m (R = 7-OMe, D = D_5). Most fortunately, compound **II**u displayed excellent antitumor activity with broad-spectrum. Its IC_{50} values against the tested six cell lines are all under 1.0 μM, identified itself as the most promising candidate. However, after the bridge CH_2 group between the DTC moiety and the chromone ring of compound **II** was removed, the antitumor activity of the resulted compound **III** reduced significantly, indicating that the flexibility of the DTC group might be a vital factor for the activity. In addition, when the DTC moiety was moved onto

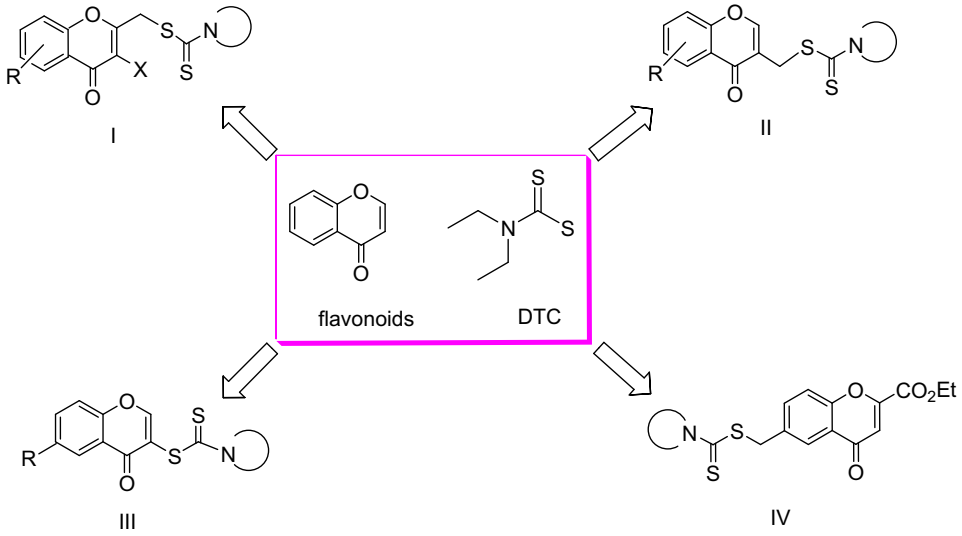

Fig. 2. Design of the title compounds.